



1. Medical Condition

GROWTH HORMONE DEFICIENCY (CHILDHOOD AND ADOLESCENT)

2. Diagnosis

A. Medical history

The history of GHD in childhood is clearly linked to short stature and a failure to meet accepted growth milestones. These features are most frequently identified by concerned parents who may initially consult their family physician. Clinical practice suggests that such parental concerns are enhanced when the child is engaged in sport and peer comparisons are frequently made.

B. Diagnostic criteria

The diagnosis of GHD in childhood requires a comprehensive clinical assessment combined with biochemical tests of the GH-IGF axis and radiological evaluation.

- 1. To authorize GHD investigation in children of short stature** one of the following criteria should be present:
 - severe short stature, defined as a height more than 3 SD below the mean.
 - height more than 1.5 SD below the mid parental height
 - height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for chronological age, or a decrease in height SD of more than 0.5 over 1 year
 - (other minor criteria as mentioned in the 2000 Consensus paper)
- 2.** In a child with a history and clinical suggestions of GHD, testing for IGF-1/IGFBP-3 levels and GH provocation tests are required. In suspected isolated GH deficiency, two GH provocation tests are required. If there is defined central nervous system pathology, irradiation, MPHD, or a genetic defect, one GH test is sufficient.

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Growth Hormone Deficiency (Childhood and Adolescent)*

3. The evaluation of spontaneous GH secretion over 12 or 24 hours can be applied in accordance with a standardized protocol when GH and IGF-1 data are in conflict (normal GH and low IGF1). It is not necessary when IGF1 is normal and GH low.
4. However there are some patients who have IGF-1/ IGFBP-3 levels below the normal range on repeated tests but GH responses in provocation tests above the cut-off level. These children have an abnormality of the GH axis and could be considered for GH treatment, despite not being classically GH deficient. In this case the response to GH treatment must be carefully reviewed by a specialist in pediatric endocrinology.

- C. Relevant medical information

- Biological markers other than the GH-IGF axis (bone density, body composition, and bone markers) are presently not considered specific enough to diagnose GHD.
- Bone age estimated from an X ray of the left wrist and hand should be undertaken as part of the routine evaluation in children. It should be read by an experienced person.
- An MRI (or CT scan) of the brain with particular attention to the hypothalamic-pituitary region may be carried out in any child diagnosed as having GHD.
- To report assay data, a clear statement of methodology is required. An assay that measures 22-kDa hGH, using monoclonal antibodies, is recommended.
- For GH provocation tests a limited number of provocative agents should be used in a well standardized protocol (arginine, clonidine, glucagons, insulin and L-Dopa, Betablockers, coupled tests) and monitored carefully by an experienced team. As an indication in a child with clinical criteria of GHD, a peak GH concentration **below 10 microg/L** is traditionally used to support the diagnosis. The criteria values should be based on the updated consensus guidelines for the diagnosis of GHD in a child (see references at the end of the document).

3. Medical best practice treatment

A. Name of prohibited substance

Recombinant hGH

B. Route

Subcutaneous injection

C. Frequency

The current dosage of GH is in the range of 25-50 mcg/kg per day with six subcutaneous injections in a week or sometimes daily.

D. Recommended duration of treatment

The treatment should be discontinued on the recommendation of the relevant specialist in charge of the case.

4. Other non-prohibited alternative treatments?

No other treatment

5. Consequences to health if treatment is withheld

Significant growth-related consequences.

6. Treatment monitoring

A routine follow up should be performed by a pediatric endocrinologist in partnership with the pediatrician or family physician on a 3-6 monthly basis. The single most important parameter in the monitoring is the growth response with height measurement and height velocity (expressed in SD for comparison). For safety and assurance of compliance, monitoring of serum IGF-1 and IGFBP-3 is useful. Values should imperatively be kept in the age-related normal range, in order to avoid any over replacement (with evaluation of bone age).

7. TUE validity and recommended review process

One year for the first approval combined with continuous clinical and biochemical monitoring of results. After one year an approval for 3 years is acceptable if recommended by specialists in charge of the patient. In this case a simplified review of the file will be required annually.

8. Any appropriate cautionary matters

Provided all the criteria for the diagnosis of GHD in childhood have been met and standards of treatment monitoring are in place there are no other significant cautionary matters. The primary objective of therapy with recombinant hGH is the normalization of growth during childhood in order to reach a normal adult height.

9. References

1. The Merck Manual, sec 2, Ch. 6, sec 19 Ch 269 Endocrine and metabolic disorders
2. Journal of Clinical Endocrinology and Metabolism Vol. 85, No 11, *Consensus Guidelines for the diagnosis and Treatment of GH Deficiency in Childhood and Adolescence*
3. American Association of Clinical Endocrinologists. *Medical Guidelines for clinical practice for growth hormone use in adults and children.* 2003 update.